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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,188	06/02/2005	Niall Gormley	2713-1-015PCT/US	1232

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,188	GORMLEY ET AL.	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 27-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed April 22, 2010. This action is made FINAL.

Claims 4 and 27-36 are currently pending.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejections were previously presented:

3. Claims 4, 27-31, and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanisn (WO 01/57248 Pub 9/2001) as evidenced by Cheeseman (US Patent 5302509 Issued 1994) and in view of Lackey (US Patent 5652126 Issued 1997) and Hong (US Patent 5747298 Issued 1998) .

Regarding Claims 4, 35, and 36 Balasubramanisn teaches a method comprising forming an array of polynucleotide molecules immobilized on a solid surface. Each polynucleotide has a hairpin loop structure wherein one end of hairpin loop structure acts as a primer and the other end of the hairpin loop structure acts as a template (page 3, lines 11-14 and page 4 line 28 to page 5 line 7). Balasubramanisn further teaches that the polynucleotides are attached to the array at a density of between 10^6-10^9 sequences per cm^2 (page 4, line 9). Balasubramanisn also teaches determining the sequence of the template nucleic acids by synthesizing a complementary nucleic acid strand. Specifically Balasubramanisn cites the method of Cheeseman as a suitable sequencing method (page 7, lines 24-31). The method of Cheeseman comprises contacting the template with fluorescently labeled 3' blocked nucleotide triphosphates, with each of the bases having a different fluorescent label and a polymerase. The DNA polymerase causes selective addition of only the complementary labeled NTP, thus identifying the next unpaired base in the unknown strand. The 3' blocking group is then removed, setting the system up for the next NTP addition and so on (Abstract). Thus Balasubramanisn as evidenced by Cheeseman teaches determining the sequence of the template nucleic acids by synthesizing a first complementary copy of each of the template sequences wherein said synthesizing involves repeated cycles of incorporating

a single nucleotide into the first complementary copy and detecting incorporation of the single nucleotide into the first complementary copy on the array thereby performing a first round of sequencing to generate a sequence of the first complementary copy.

Regarding Claims 27 and 28 Balasubramanisn teaches a method wherein the template polynucleotides are attached to a double stranded anchor wherein the double stranded anchor is a self complementary hairpin (page 4 line 28 to page 5 line 7).

Regarding Claim 30 Balasubramanisn teaches that the 10^6-10^9 different templates are individually resolvable (page 4, line 11).

Regarding Claim 31 Balasubramanisn teaches a method wherein the sequencing determination is carried out using cycles of incorporation and detection of fluorescently labeled nucleotides. Specifically Balasubramanisn refers to the method of Cheeseman which teaches this (see Cheeseman abstract).

Regarding Claim 33 Balasubramanisn teaches a method which employs a polymerase enzyme to synthesize a complementary strand one base at a time. Specifically Balasubramanisn cites the method of Cheeseman which teaches using Taq polymerase (see Cheeseman Col 3, line 67).

Further regarding claim 35 it is noted that the recitation of “a method for simultaneously sequencing a complete genome” merely sets forth the intended purpose of the claimed method, but does not limit the scope of the claims. As noted in the MPEP 211.02, “ a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where

the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, the process steps are able to stand alone and the preamble limitation is not accorded patentable weight.

Balasubramanisn does not teach a method further comprising removing the complementary copy of each of the template sequences from the array thereby regenerating the immobilized single stranded template molecules on the array (clms 4, 35, and 36 (step c)). Further Balasubramanisn does not teach performing a second round of sequencing of each of the immobilized single stranded template nucleic acid molecules regenerated in step (c) by synthesizing a second complementary copy of each of the template sequences, wherein said synthesizing involves repeated cycles of incorporating a single nucleotide into the second complementary copy and detecting incorporation of the single nucleotide into the second complementary copy on the array, thereby generating a sequence of the second complementary copy (clms 4, 35, and 36 (step d)). Balasubramanisn does not teach comparing the sequence of the first complementary copy detected in step (b) to the sequence of the second complementary copy detected in step (d) for each of the immobilized single stranded template nucleic acid molecules to confirm sequencing data of each of the immobilized single stranded

template nucleic acid molecules (clms 4, 35, and 36 (step e)). Balasubramanisn does not teach a method wherein the double stranded anchor comprises a recognition site for a restriction endonuclease (clm 29). Further Balasubramanisn does not teach a method wherein the comparing step reduces random sequencing errors of the template sequences arising from the first round of sequencing (clm 34).

However Lackey teaches a method that comprises synthesizing a complementary copy of a nucleic acid sequence using a primer and a template sequence. Lackey further teaches that in instances where a DNA primer/template with a single 3' ribonucleotide is used, cleavage at the ribonucleotide residue, followed by separation and purification of the oligonucleotide product, results in a fully regenerated and reusable primer/template (Col 13, lines 26-31). Lackey further teaches that cleavage may be performed using a site specific restriction endonuclease, alkaline hydrolysis or an endonuclease such as RNase (col 12, lines 42-47). Thus Lackey teaches a method comprising removing the complementary copy of a template sequence thereby regenerating the template and a method wherein the primer has a recognition site for a restriction endonuclease.

Additionally Hong teaches that researchers in the field of DNA sequencing often have to use several approaches to confirm their findings in order to avoid being misled by potentially erroneous sequence data. Hong teaches that sometimes researchers rely on repeating the same sequencing experiment with different DNA polymerases, or performing another sequencing reaction with the template that is complementary to the first single stranded DNA template, and comparing the results for possible

discrepancies (Col 2, lines 47-55). Thus Hong teaches performing a second round of sequencing on the same template used in the first round of sequencing and comparing the sequence of the first complementary copy to the sequence of the second complementary copy in order to confirm sequence data. Since possible discrepancies were noted the method of Hong is being interpreted as a method that reduces random sequencing errors.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn by removing the first complementary strand to regenerate the template molecule (as suggested by Lackey), resequencing the template molecule (as suggested by Hong), and comparing the sequence of the first complementary copy and the second complementary copy to confirm sequence data (as suggested by Hong). Hong teaches that researchers in the field of DNA sequencing often have to use several approaches to confirm their findings in order to avoid being misled by potentially erroneous sequence data. Based on this teaching one of skill in the art performing the method of Balasubramanisn would have been motivated to remove the first complementary strand to regenerate the template molecule, resequence the regenerated template molecule, and compare the two sequences in order confirm their findings and avoid being misled by potentially erroneous sequence data. One of skill in the art would have had a reasonable expectation of success in doing so. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention as a

whole was prima facie obvious to one or ordinary skill in the art at the time the invention was made, as evidenced by the references.

4. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanisn (WO 01/57248 Pub 9/2001) as evidenced by Cheeseman (US Patent 5302509 Issued 1994) and in view of Lackey (US Patent 5652126 Issued 1997) and Hong (US Patent 5747298 Issued 1998) as applied to claims 4 and 31 above and in further view of Barnes (WO 01/57249 Pub 8/2001).

The teachings of Balasubramanisn (evidenced by Cheeseman), Lackey, and Hong are presented above.

The combined references do not teach a method wherein the fluorescently labeled nucleotides are detected using a microscope with total internal reflection based imaging.

However Barnes teaches that using total internal reflection fluorescent microscopy it is possible to achieve wide field imaging with single polymer sensitivity. This allows arrays of greater than 10^7 resolvable polymers per cm^2 to be used (page 6, lines 9-14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn (as evidenced by Cheeseman), Lackey, and Hong by using a microscope with total internal reflection to detect the incorporation of each fluorescently labeled nucleotide as suggested by Barnes. Barnes teaches it is possible to achieve wide field imaging with

single polymer sensitivity and that this allows arrays of greater than 10^7 resolvable polymers per cm^2 to be used. Therefore one of skill in the art would have been motivated to use the detection method disclosed by Barnes for the benefit of being able to detect a large number of individual fluorescent nucleotides present on the array.

Response To Arguments

5. In the response filed April 22, 2010, the Applicants traversed the rejections based on the combination of Balasubramanisn (WO 01/57248 Pub 9/2001), as evidenced Cheeseman (US Patent 5302509 Issued 1994), in view of Lackey (US Patent 5652126) and Hong (US Patent 5747298).

The Applicants argue that the combination of references fail to teach or suggest performing a second round of each of the immobilized single-stranded template nucleic acid molecules regenerated in step (c) and comparing the sequence of the first complementary copy detected in step (b) to the sequence of the second complementary copy detected in step (d) for each of the immobilized single-stranded template nucleic acid molecules to confirm sequencing data of each of the immobilized single-stranded template nucleic acid molecules. This argument has been fully considered but is not persuasive. Applicants are reminded that this is a 103 rejection and a combination of references has been relied upon to teach these elements. In the instant case Balasubramanisn teaches sequencing immobilized single stranded template nucleic acid molecules (page 7, lines 24-31). Lackey teaches synthesizing a complementary copy of a nucleic acid sequence using a primer and a template and

further teaches removing the complementary copy of the template thereby regenerating the template (col 13, lines 26-31). Hong teaches that sometimes researchers rely on repeating the same sequencing experiment with different DNA polymerases or performing another sequencing reaction with the template that is complementary to the first single stranded DNA template, and comparing the results for possible discrepancies (Col 2, lines 47-55). Thus the combination of references teaches each of the claimed steps.

The fact that Lackey is silent with respect to sequencing is irrelevant. While Lackey may not be directed to "sequencing" per se, Lackey is not being relied upon to teach "sequencing" because it is taught by Balasubramanisn. The method of Lackey is relevant to the instant claims because the method of Lackey comprises synthesizing a complementary nucleic acid sequence using a template sequence and a primer that has a recognition site for a restriction enzyme and then cleaving the primer at the recognition site, thereby producing a fully regenerated and reusable primer/template. The present claims also require synthesizing a complementary copy of a template and removing the complementary copy of a template thereby regenerating the original template.

The argument that Hong does not perform a second round of sequencing on the same template used in the first round of sequencing is also not persuasive. As stated above Hong teaches that sometimes researchers rely on repeating the same sequencing experiment with different DNA polymerases or performing another sequencing reaction with the template that is complementary to the first single stranded

DNA template, and comparing the results for possible discrepancies (Col 2, lines 47-55). In the instant case "repeating the same sequencing experiment with different DNA polymerases" can be interpreted as repeating a second round of sequencing on the same template used in the first round of sequencing since this implies that everything except for the polymerase is the same. Regarding the preferred embodiments of Hong which Applicants refer to in their arguments it is noted that the MPEP 2123 states that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including non preferred embodiments. The MPEP further states that the use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are a part of the literature of the art, relevant for all they contain. Thus the fact that Hong discloses sequencing a first pool of template nucleic acid molecules and then resequences a second pool of template molecules is irrelevant because based on the teachings in the background section (see for example Col 2, lines 47-55) Hong teaches and/or suggests performing a second round of sequencing on the same template used in the first round of sequencing.

The argument that the method of Hong pertains to gel based sequencing and is not capable of yielding any information that can be ascribed to a particular template molecule in a population is also not persuasive. In the instant case the elements missing from Hong are taught by Balasubramanisn. Specifically Balasubramanisn teaches sequencing immobilized single stranded template nucleic acid molecules (page 7, lines 24-31). The sequencing method disclosed by Balasubramanisn is the same

sequencing method disclosed in the instant application and does not rely on the use of gels. Further the method of Balasubramanisn is capable of yielding information that can be ascribed to a particular template molecule in the population since the template nucleic acid molecules are present on an array. As stated above Hong is only being relied upon for performing a second round of sequencing on the same template used in the first round of sequencing and comparing the sequence of the first complementary copy to the sequence of the second complementary copy in order to confirm sequence data. Hong specifically states that sometimes researchers rely on repeating the same sequencing experiment with different DNA polymerases (Col 2, lines 47-55). Thus Hong teaches repeating the same sequencing experiment (i.e., the sequencing experiment of Balasubramanisn) using all of the same reagents, including the same template, except for the polymerases.

The argument that the Office has failed to provide a rationale to support the contention that it would have been obvious for an ordinary skilled practioner to combine the methods to arrive at the present invention has been considered but is not persuasive. In the instant case motivation is present and has been provided. In the instant case, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn by removing the first complementary strand to regenerate the template molecule (as suggested by Lackey), resequencing the template molecule (as suggested by Hong), and comparing the sequence of the first complementary copy and the second complementary copy to confirm sequence data (as suggested by Hong). Hong teaches that researchers in the

field of DNA sequencing often have to use several approaches to confirm their findings in order to avoid being misled by potentially erroneous sequence data. Based on this teaching one of skill in the art performing the method of Balasubramanisn would have been motivated to remove the first complementary strand to regenerate the template molecule, resequence the regenerated template molecule, and compare the two sequences in order confirm their findings and avoid being misled by potentially erroneous sequence data. One of skill in the art would have had a reasonable expectation of success in doing so. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention as a whole was prima facie obvious to one or ordinary skill in the art at the time the invention was made, as evidenced by the references. The Applicants argument that there is no rational to explain why an ordinarily skilled artisan would modify the method of Balasubramanisn to add the step of removing the first complementary strand to regenerate the template molecule is misleading. Based on the teachings of Hong one of skill in the art would have recognized that resequencing was desirable due to the fact that sequencing errors occur and based on the teachings of Lackey one of skill in the art would have recognized that it was possible remove the first complementary strand and regenerate a template molecule which could be used for resequencing.

Regarding the rejection over claim 32 the Applicants argue that Barnes does not cure the deficiencies of the other references.

This argument has been fully considered but is not persuasive. The applicants

arguments regarding what is missing in Balasubramanisn (as evidenced by Cheeseman), Lackey, and Hong have been fully addressed above. The response to applicant's arguments, as set forth above, applies equally to the present ground of rejection.

Conclusion

6. **No claims are allowed.**

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Stephen Kapushoc/
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